

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/155, 45/00	A1	(11) International Publication Number: WO 97/23203 (43) International Publication Date: 3 July 1997 (03.07.97)
(21) International Application Number: PCT/EP96/05870 (22) International Filing Date: 18 December 1996 (18.12.96) (30) Priority Data: 9526330.7 22 December 1995 (22.12.95) GB 9624914.9 29 November 1996 (29.11.96) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): TURNER, Nicholas, Charles [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). PIERCY, Valerie [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: AMINO GUANIDINE FOR TREATING NIDDM (57) Abstract A method for the treatment and/or prophylaxis of Type II diabetes, which method comprises the administration, to a human or non-human mammal, of an effective non-toxic pharmaceutically acceptable amount of an inhibitor of protein glycation, such as aminoguanidine. Preferably, the invention provides a method for the prophylactic treatment of Type II diabetes, in particular delaying or preventing the progression from hyperinsulinaemia to hyperglycaemia.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

AMINO GUANIDINE FOR TREATING NIDDM

5 This invention relates to a novel method for the treatment of and/or prophylaxis of non-insulin dependant (NIDDM or Type II) diabetes, and in particular to the use of an inhibitor of protein glycation, such as aminoguanidine, for the said treatment and/or prophylaxis.

Hydrazinecarboximidamide (hereinafter 'aminoguanidine') is a known compound (Journal of American Chemical Society, 57, 2730, (1935)).

10 Aminoguanidine is known to be an NO synthase inhibitor (Eur. J Pharmacol., 233, 119-125).

Aminoguanidine is also known to be an inhibitor of protein glycation and such activity is considered to be closely linked to the activity of aminoguanidine in the treatment of diabetic complications and other conditions associated with advanced glycosylation end products (J Carbohydrate Chem., 12(6), 731-742, (1993), Diabetes, 41, January 1992, 26-29, European
15 Patent Application, publication number 0339496 and United States Patent numbers 5128360 and 5238963). Indeed aminoguanidine is under evaluation in animal models for the treatment of diabetic complications (Diabetes 42, 221-232 1993 and Diabetologia, 35, 946-950).

To date there has been no indication that aminoguanidine or any other inhibitor of protein glycation would have a beneficial effect on Type II diabetes itself. As indicated above the
20 emphasis has been focused upon the complications of diabetes. We have now discovered that aminoguanidine does show potential for use in the treatment and/or prophylaxis of Type II diabetes. In particular, aminoguanidine is indicated to delay or prevent the progression of non-insulin dependent diabetes from hyperinsulinaemia to overt diabetes. This novel and surprising effect is considered to be due to the inhibition of protein glycation by aminoguanidine.

25 Accordingly, the present invention provides a method for the treatment and/or prophylaxis of Type II diabetes, which method comprises the administration, to a human or non-human mammal, of an effective non-toxic pharmaceutically acceptable amount of an inhibitor of protein glycation, such as aminoguanidine or a pharmaceutically acceptable derivative thereof.

30 Preferably, the invention provides a method for the prophylactic treatment of Type II diabetes, in particular delaying or preventing the progression from hyperinsulinaemia to hyperglycaemia.

Suitable, inhibitors of protein glycation include protein and non-protein compounds, such as aminoguanidine and its derivatives or analogues, for example those disclosed in International Patent Application publication number WO 94/11490, European Patent Application, publication
35 number 0339496 or hydrazines and hydrazides such as those disclosed in WO 94/11490 and

United States Patent numbers 5218360 and 5238963; thiosemicarbazides such as those disclosed in Japanese Patent Application publication number 01056614; non-hydrazine glycation inhibitors such as the derivatives of pyridine N-oxide disclosed in JP08175995; crosslink breakers such as phenacylthiazolium bromide and its derivatives or analogues as disclosed in Nature,
5 1996;382:211-278; and the amino acid/protein derivatives disclosed in International Patent Application publication number 93/04690; the contents of the publications listed in this paragraph are incorporated herein by reference.

When used herein a 'protein glycation inhibitor' refers to an agent which inhibits the non-enzymatic glycation or glycosylation of proteins and glycoproteins (the Maillard reaction), or
10 which prevent the formation of irreversible advanced glycation end-products, or which prevents the crosslinking of advanced glycation end-products or which cleave advanced glycation end-product cross links.

The protein glycation inhibition activity of a compound is assessed in conventional tests such as inhibition of the glycation of haemoglobin or other suitable protein (Analytical
15 Biochemistry;1988:175:347-360).

A suitable pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof.

Suitable pharmaceutically acceptable salts include acid addition salts.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as
20 the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, a-keto glutarate and a-glycerophosphate, especially the maleate salt.

Suitable pharmaceutically acceptable solvates include hydrates.

25 The protein glycation inhibitors of the invention may be prepared according to conventional methods, such as the methods disclosed in the above mentioned publications including the publications incorporated herein by reference, for example aminoguanidine may be prepared according to the methods disclosed in J. Amer. Chem. Soc. 57,2730, (1935).

Salts and/or solvates may be prepared and isolated according to conventional procedures.

30 In a further aspect the present invention also provides protein glycation inhibitor such as aminoguanidine or a pharmaceutically acceptable derivative thereof, for use in the treatment of and/or prophylaxis of Type II diabetes.

There is also provided an inhibitor of protein glycation, such as aminoguanidine or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for
35 the treatment and/or prophylaxis of Type II diabetes.

In the above mentioned treatment and/or prophylaxis the protein glycation inhibitor, such as, aminoguanidine or a pharmaceutically acceptable derivative thereof may be administered per se or preferably as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

5 Accordingly, the present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of Type II diabetes, which composition comprises a protein glycation inhibitor, such as aminoguanidine or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds,
10 compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral
15 administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

20 In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl
25 sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

Conveniently, the active ingredient may be administered as a pharmaceutical composition
30 hereinbefore defined, and this forms a particular aspect of the present invention.

In the above mentioned treatments the active compound, may be taken in doses such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg, generally about 0.5 to 10 mg. That is in the range of from 1.429×10^{-3} to 85.714

mg/kg/day, more usually about 1.429×10^{-2} to 21.429 mg/kg/day, generally about 7.143×10^{-3} to 0.1429 mg/kg/day.

No unacceptable toxicological effects are observed when active compounds are administered in accordance with the above mentioned invention.

5 The following Example illustrates the invention but does not limit it in any way.

EXAMPLE**Methodology of dbdb mouse model**

- 5 The obese db/db mouse is a genetic model of type 2 non-insulin dependent diabetes which is both insulin resistant and hyperglycaemic. Male animals were obtained at 6 weeks of age. Blood samples were taken by tail tip snip for measurement of pre-treatment blood glucose. Animals were allocated into treated and control groups such that the mean and standard deviation of the fasting blood glucose concentrations of each group was similar.

10

- On day 0 of the study a group of obese animals and their lean litter mates were killed for measurement of baseline biochemistry and histology. In addition one group of animals (control; $n = 14$) were fed a standard diet and a further group received aminoguanidine (500mg/kg; $n = 14$) in the same diet. Animals were allowed free access to food and water and their intake measured daily. At weekly intervals 24hr urine output was also measured. Mice ($n = 7$) were killed at 30 days and 85 days from commencement of treatment. Blood was taken for measurement of glucose and insulin concentrations and the pancreas removed for histological analysis and for measurement of pancreatic insulin.

20 **Data from dbdb mouse model**

Food intake and body weight gain of the control and treated groups was similar throughout the experimental period.

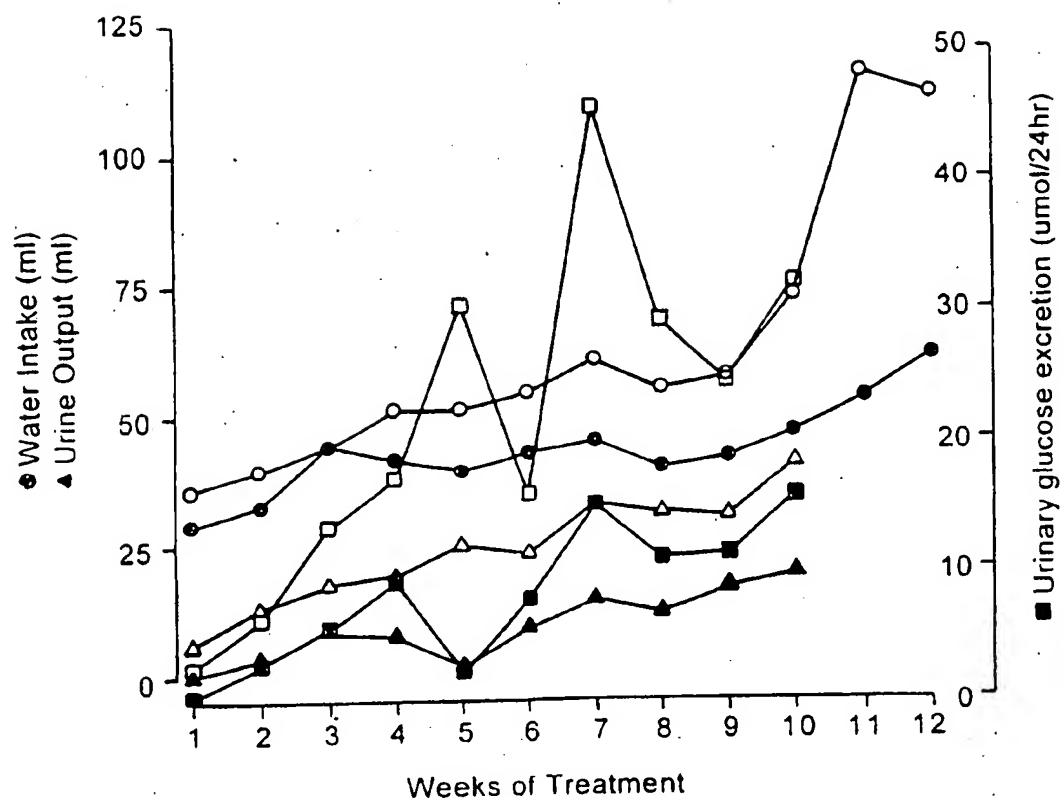
- Immediately prior to dosing obese animals were normoglycaemic (blood glucose 10.4 ± 0.97 mM) but were hyperinsulinaemic compared to their lean litter mates (serum insulin 127 ± 37 ng/ml in obese animals 3.05 ± 1.03 ng/ml in leans). By day 30 of the dosing period the obese control group were hyperglycaemic (blood glucose 24.9 ± 1.0 mM) and had markedly lower serum insulin levels (30.75 ± 4.3 mM) compared to the pre-treatment values. By day 85 of the treatment period, fasting blood glucose had risen to 28.1 ± 2 mM and serum insulin concentrations had fallen further, to 11.7 ± 1.8 ng/ml. Aminoguanidine attenuated the fall in fasting insulin concentrations (58.3 ± 13 ng/ml on day 30, 23.3 ± 4.1 ng/ml on day 85) and on day 85 had significantly reduced the prevailing fasting hyperglycaemia (21 ± 1.7 mM). Pancreatic insulin content of the aminoguanidine treated group of obese animals was twice that of the untreated animals (64.3 ± 17.8 ng/mg pancreas compared to 30.0 ± 2.6 ng/mg, respectively). From day 63 of the experimental period obese control animals were markedly

polydipsic and polyuric compared to day 7. This increase in water intake and urine output is a characteristic of diabetes (hyperglycaemia) and was prevented by treatment with aminoguanidine (Figure 1). Similarly urinary glucose excretion increased steadily over the experimental period, in both untreated and treated animals, but from day 35 was lower in the
5 aminoguanidine treated group (Figure 1). The development of diabetes (hyperglycaemia) was associated with changes in islet morphology, and the islets of untreated control animals were markedly hypertrophic, disorganised and had irregular boundaries. On day 85 loss of β -cells and inward collapse of the islet was evident. Islet insulin content was markedly depleted. On day 30 and 85 of the treatment period these changes in islet morphology were
10 partially ameliorated.

Claims

1. A method for the treatment and/or prophylaxis of Type II diabetes, which method comprises the administration, to a human or non-human mammal, of an effective non-toxic
5 pharmaceutically acceptable amount of an inhibitor of protein glycation.
2. A method according to claim 1, for the prophylactic treatment of Type II diabetes.
3. A method according to claim 1 or claim 2, for delaying or preventing the progression from
10 hyperinsulinaemia to hyperglycaemia.
4. A method according to any one of claims 1 to 3, wherein the protein glycation inhibitor is selected from aminoguanidine and its derivatives or analogues, hydrazine type compounds and hydrazide derivatives, thiosemicarbazides, derivatives of pyridine N-oxide and crosslink breakers
15 such as phenacylthiazolium bromide and its derivatives or analogues.
5. A method according to any one of claims 1 to 4, wherein the protein glycation inhibitor is aminoguanidine.
- 20 6. A protein glycation inhibitor, or a pharmaceutically acceptable derivative thereof, for use in the treatment of and/or prophylaxis of Type II diabetes.
7. The use of a protein glycation inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of Type II
25 diabetes.
8. A pharmaceutical composition for the treatment and/or prophylaxis of Type II diabetes, which composition comprises a protein glycation inhibitor, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.
30

open symbols = db/db Control
solid symbols = Aminoguanidine



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 96/05870

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/155 A61K45/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 12800 A (UPJOHN CO) 5 September 1991 * see in particular page 6, lines 15-31, examples 1 and 2, and page 8, lines 18-22* ---	1-4,6-8
X	US 5 238 963 A (CERAMI ANTHONY ET AL) 24 August 1993 cited in the application * see in particular col. 8-10 and examples VIII-X * ---	1,2,4-8
P,X	WO 96 16301 A (MCDUGALL GREGORY J) 30 May 1996 *see in particular page 7, line 8 -page page 10, line 22. Tables 6-8 * -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 April 1997

Date of mailing of the international search report

23.05.97

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Isert, 8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9112800 A	05-09-91	AT 141505 T	15-09-96
		AU 645076 B	06-01-94
		AU 7485091 A	18-09-91
		CA 2073873 A,C	29-08-91
		DE 69121561 D	26-09-96
		DE 69121561 T	30-01-97
		EP 0517820 A	16-12-92
		EP 0713699 A	29-05-96
		ES 2090317 T	16-10-96
		JP 8020534 A	23-01-96
		JP 8025875 B	13-03-96
		JP 5505189 T	05-08-93
		AU 7316591 A	18-09-91
		NZ 237249 A	27-09-94
		WO 9112799 A	05-09-91
		US 5599841 A	04-02-97
		US 5132324 A	21-07-92
		US 5134164 A	28-07-92
US 5238963 A	24-08-93	US 5128360 A	07-07-92
		US 4665192 A	12-05-87
		US 4758583 A	19-07-88
		US 5468777 A	21-11-95
		US 5334617 A	02-08-94
		US 5399560 A	21-03-95
		US 5318982 A	07-06-94
		US 5358960 A	25-10-94
		US 5326779 A	05-07-94
		US 5476849 A	19-12-95
		US 5514676 A	07-05-96
		US 5534540 A	09-07-96
		US 5218001 A	08-06-93
		US 5254593 A	19-10-93
		US 5272176 A	21-12-93
		AU 583034 B	20-04-89
		AU 4153185 A	11-10-85
		CA 1250587 A	28-02-89
		CA 1294218 A	14-01-92
		DE 3587667 D	05-01-94
		DE 3587667 T	17-03-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5238963 A		EP 0175764 A	02-04-86
		EP 0322402 A	28-06-89
		JP 5172813 A	13-07-93
		JP 61501706 T	14-08-86
		US 5316754 A	31-05-94
		WO 8504169 A	26-09-85
		US 4900747 A	13-02-90
		US RE35465 E	25-02-97
		US 5612332 A	18-03-97
		US 5175192 A	29-12-92
		US 5128122 A	07-07-92
		US 5140048 A	18-08-92
		US 5096703 A	17-03-92
		US 5106877 A	21-04-92
		US 5114943 A	19-05-92
		US 5258381 A	02-11-93
		US 5130324 A	14-07-92
		US 5130337 A	14-07-92
		US 5585344 A	17-12-96
		US 5202424 A	13-04-93
		US 5221683 A	22-06-93
		US 5288615 A	22-02-94
		US 5356895 A	18-10-94
		US 5243071 A	07-09-93
		US 5262152 A	16-11-93
		US 5272165 A	21-12-93
		AT 112165 T	15-10-94
		AU 610056 B	16-05-91
		AU 6495886 A	21-05-87
<hr/>			
WO 9616301 A	30-05-96	AU 3876995 A	17-06-96
<hr/>			

WORLD
INTELLECTUAL
PROPERTY
ORGANIZATION



IP SERVICES

Home IP Services PatentScope Patent Search



Search result: 1 of 1

(WO/1997/023203) AMINO GUANIDINE FOR TREATING NIDDM

Biblio. Data Description Claims National Phase Notices Documents

Latest published bibliographic data

Publication No.: WO/1997/023203

International Application No. PCT/EP1996/005870

Publication Date: 03.07.1997

International Filing Date: 18.12.1996

Int. Class.⁸: A61K 31/00, A61K 31/155.

Applicant: SMITHKLINE BEECHAM PLC TURNER, Nicholas, Charles PIERCY, Valerie.

Inventor: TURNER, Nicholas, Charles PIERCY, Valerie.

Priority Data: 9526330.7 22.12.1995 GB

Title: (EN) AMINO GUANIDINE FOR TREATING NIDDM

(FR) AMINO GUANIDINE POUR LE TRAITEMENT DU DIABETE DE TYPE II

Abstract: (EN) A method for the treatment and/or prophylaxis of Type II diabetes, which method comprises the administration, to a human or non-human mammal, of an effective non-toxic pharmaceutically acceptable amount of an inhibitor of protein glycation, such as aminoguanidine. Preferably, the invention provides a method for the prophylactic treatment of Type II diabetes, in particular delaying or preventing the progression from hyperinsulinaemia to hyperglycaemia.

(FR) L'invention concerne un procédé pour le traitement et/ou la prophylaxie du diabète de type II, ledit procédé consistant à administrer à un mammifère humain ou non, une quantité efficace, non toxique et pharmaceutiquement acceptable, d'un inhibiteur de la glycosylation de protéines, tel que l'aminoguanidine. De préférence, l'invention concerne un procédé pour le traitement prophylactique du diabète de type II, en particulier pour retarder ou empêcher la progression de l'hyperinsulinémie vers l'hyperglycémie.

Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, KE, LS, MW, SD, SZ, UG, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG.